Going beyond Lifespan in Comparative Biology of Aging

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Viewpoint

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ABSTRACT

Over the last few decades, comparative biology of aging has aimed to identify factors responsible for the huge variability in lifespan observed across the animal kingdom. While these studies have undeniably improved our understanding of the complex processes that shape lifespan, we argue that time has now come to focus on specific aging metrics (e.g., age at the onset of aging, rate of aging) rather than on lifespan. Such a shift in research programs would help decipher the fine-scale mechanisms shaping age-specific mortality profiles across the tree of life.

KEYWORDS: biogerontology; comparative biology; demography; senescence

THE COMPARATIVE BIOLOGY OF AGING

Lifespan is one of the most variable life history traits in the animal kingdom, lasting from days to centuries (e.g., Nielsen et al. 2016 [1]). This huge variability has fascinated the scientific community for a very long time and a large body of research has been devoted to the identification of its evolutionary roots, as well as its biological underlying mechanisms. Among the ecological and biological correlates of lifespan across species, body mass is undeniably one of the most important. Many comparative studies have demonstrated that lifespan is closely associated with body size according to an allometric relationship (i.e., Ln(Longevity) = Ln(α) + βLn(Body Size), with Ln(α) being the allometric intercept and β being the allometric exponent) with an allometric exponent generally close to 0.25 when body mass is used as a measure of body size (Lindstedt & Calder 1981 [2]). As body mass explains a large amount of the observed variation in lifespan, species that break this relationship, such as bats (e.g., Brandt's bat, *Myotis brandti*) or naked mole rats (*Heterocephalus glaber*) (see Austad 2010 [3] for a review) are highly valuable models for biomedical researchers who seek to crack the mysteries of extreme longevity (e.g., Gorbunova et al., 2014 [4]). Most comparative biology of aging research

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performed in biogerontological science aims to identify genetic, cellular or physiological correlates of lifespan, once accounting for the allometric scale and the phylogenetic relatedness across species. So far, these comparative analyses have been insightful, highlighting for example the key role played by biochemical and genetic factors (e.g., Ma et al., 2015 [5]). However, we argue here that time has come to not only focus investigations on lifespan as a metric of aging, but to embrace the full pattern of age-specific mortality displayed by organisms.

FROM LIFESPAN TO DEMOGRAPHIC AGING

The maximum lifespan is the most popular metric used in comparative biology of aging, mostly because this information is available for most species and can be rapidly compiled at broad taxonomic levels (see Lemaître et al., 2014 [6] for an example in mammals). Yet, this metric simply corresponds to the extreme value observed in a single individual, and is highly dependent of the sample size. Moreover, as extreme values do not reliably reflect trait distributions, the maximal lifespan is not representative of the distribution of the ages at death in a given species (Ronget & Gaillard 2020 [7]). This is notably well illustrated in humans, in which the extreme longevity of Jeanne Calment (122 years old) is often claimed to be non-representative of the entire population. Moreover, the maximum lifespan and more generally any lifespan metric (i.e., life expectancy, median lifespan) does not account for the complex shape of age-specific mortality and its relevance is therefore limited when it comes to study demographic aging (Brunet-Rossinni & Austad 2006 [8]; Holmes & Martin 2009 [9]).

From a demographic point of view, aging (or actuarial senescence) is defined as the increase of mortality rate with age. Initially observed in human populations (Gompertz 1825 [10]), there is now compelling evidence (especially from case studies in birds and mammals) that the aging process constitutes the rule rather than the exception in natural environments (Nussey et al., 2013 [11]). Interestingly, the increase in long-term ecological studies has now made age-specific demographic data available for a large number of vertebrate species. Once demographic data are available, the challenge is to assess accurately the aging patterns. For this purpose, two metrics are generally considered: the age at the onset of aging (i.e., a measure of the *timing* of aging) and the rate of aging (i.e., a measure of the *tempo* of aging) (Figure 1). Historically, most research has focused on the rate of aging simply because pioneering theoretical work assumed that the onset of aging should be set at the age at first reproduction (e.g., Williams 1957 [12]). Recent literature on aging in the wild has totally changed this view (Gaillard & Lemaître 2017 [13]) and it is now widely accepted that both age at the onset of aging and rate of aging vary a lot across species relative to the age at first reproduction (Gaillard & Lemaître 2017 [13]). Many modeling approaches have now been proposed to fit age-specific mortality patterns (e.g., Gompertz function,

Weibull function) and most of them include parameters that are relatively easy to interpret in terms of onset or rate of aging (Ronget & Gaillard 2020 [7]).

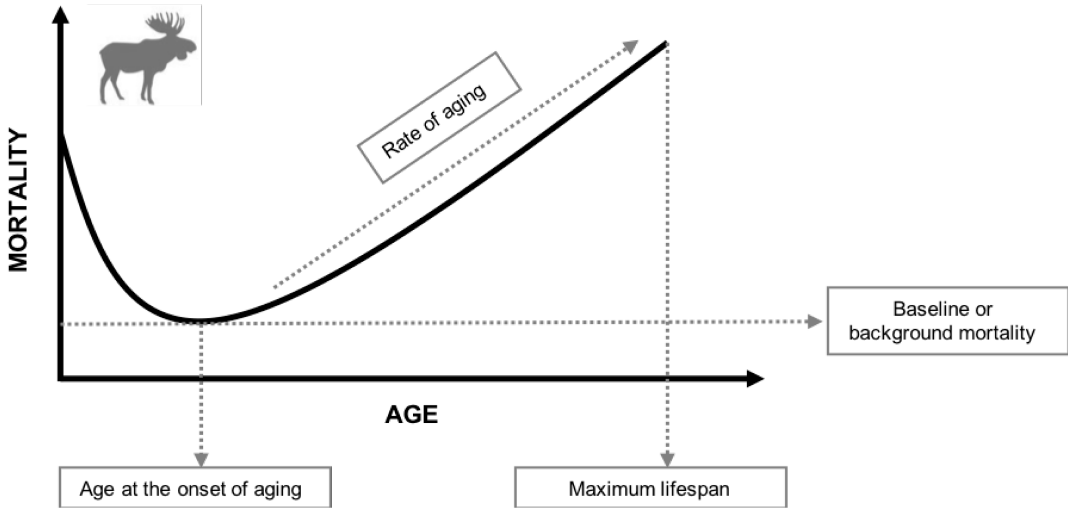

Figure 1. Age-specific mortality curve for a typical mammalian species. Mortality decreases from birth to early adulthood, then stays relatively constant at a level generally called basal or background mortality and finally starts to increase until the maximum age observed in the population (maximum lifespan). The age when mortality starts to increase is defined as the age at the onset of aging and can vary substantially across species. The rate of aging corresponds to the increase in the mortality rate with age.

Importantly, lifespan and aging metrics convey different information. For instance, a recent comparative study highlighted that the rate of aging and the lifespan can be largely uncoupled across mammals (Péron et al., 2019 [14]). This analysis revealed that the rate of aging accounts only modestly for the observed variation in mammalian lifespan. Indeed, even though the proportion of variation in longevity that is accounted for by the rate of aging increases with the species body mass, it remains consistently less than 50% of the total variation observed in lifespan (Péron et al., 2019 [14]). Therefore, any cellular or physiological function identified as a good predictor of lifespan across species cannot automatically be used as a good predictor of the rate of aging or of the age at onset of aging.

Biological constraints lead some aging metrics to be highly associated and inter-dependent. For instance, the age at the onset of aging and the lifespan are both measured in time units and contribute to the definition of the pace of life (Baudisch 2011 [15], Ronget and Gaillard 2020 [7]). The rate of aging (a measure of the extinction risk of the population) negatively covaries with this pace of life simply because at a given rate of aging, there is a greater risk of extinction in short-lived species than in long-lived species. To assess the shape of the age-specific mortality pattern independently of the influence of the pace of life, one needs to scale the age range over which aging occurs to the whole lifespan. Hence, the rate of aging over a specific proportion of lifespan spent provides a proper shape metric of the mortality pattern (Ronget & Gaillard 2020 [7]).

USE OF DEMOGRAPHIC AGING METRICS IN COMPARATIVE BIOGERONTOLOGY

On one hand, the use of the comparative approach to uncover genetic and cellular predictors of cross-species lifespan and disease has been increasing, indicating that species with the longest lifespans have evolved unique genes and metabolomic patterns. Identification of these traits has been coupled with manipulative work to show that the overexpression of specific genes can increase cellular stress resistance, indicating a causal role of these factors in regulating cell senescence and ultimately species lifespan (e.g., Sulak et al., 2016 [16]). On the other hand, the few comparative analyses that focused on aging metrics per se (rate of aging, age at the onset of aging) have mostly been performed in an evolutionary ecology framework and have revealed the key role played by body mass and also by the speed of the life history (i.e., the species position along the slow-fast continuum of life histories) (e.g., Garratt et al., 2013 [17]). Here, we hypothesize that detailed analyses of the cellular traits and genetic variation that explain aging patterns, and the analyses of both pace and shape dimensions could provide key insights into the change in age-specific mortality risks. As datasets including demographic data are now increasingly available for many animal species, we deeply encourage the biomedical community to embrace this promising avenue of research. Moreover, once accurate age-specific data on causes of death will be available for a wide spectrum of species, such approaches will also enable to investigate how species-specific cellular or physiological processes modulate the age-specific risk of contracting aging-associated diseases and to assess the contribution of these diseases to the demographic aging patterns (see Lemaître et al., 2020 [18]). This will in return provide valuable information on the biological and ecological roots of age-specific dysregulation across species.

AUTHOR CONTRIBUTIONS

JFL, MG and JMG wrote the paper.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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